REMARKS

With entry of this amendment, claims 1-21 are pending in the application. Claims 1-11 were previously withdrawn from consideration, with traverse and reservation to pursue the subject matter of the withdrawn claims in a related application in response to a Restriction Requirement (Paper No./Mail Date 09212004).

Patentability Under 35 USC § 103

Claims 12-21 are rejected under 35 USC § 103(a) as allegedly unpatentable over Media Release (Novermber 4, 2002) in view of Hirsh et al. (US 2003/0035839 A1). The Office relies upon Media Release for announcing positive phase II results for ocinaplon "as a novel anti-anxiety product in its therapeutic use for generalized anxiety disorders." (Office Action at p. 3). Media Release is further cited by the Office as allegedly teaching that "controlled release ocinaplon administered twice or three times a day is effective in the treatment of patients with generalized anxiety disorders." (id.)

The Office concedes that Media Release "does not teach the two separate compartments each containing ocinaplon with specific amounts with rapid release in first compartment and sustained release in second compartment with hydrophilic polymeric matrix (hydtroxypropyl methyl cellulose) in a unit dose, carriers such as lactose and a particle size." (Office Action at pp. 3-4)

The Office further relies upon Hirsh et al. as a secondary reference for allegedly a "new pharmaceutical composition in unit dosage form comprising anxiolytic in two different portions comprising immediate (outer layer) as well as sustained release (core)." (Office Action at p. 4). Based on these and other alleged teachings of Hirsh et al., the Office concludes that it would have been obvious to modify the above-noted, limited teachings of Media Release regarding a controlled release formulation of by providing the ocinaplon in a "unit dosage form comprising two portions as taught by Hirsh et al." (id.) More specifically, the Office contends that persons skilled in the art "would have been motivated to make such a modification in order to achieve the advantage of two portion comprising immediate as well as sustained release to improve prolonged therapeutic benefit and improve the compliance as taught by Hirsh et al." (id.)

With respect to additional subject matter recognized by the Office as not being disclosed by either Media Release nor Hirsh et al., the Office provides a blanket assertion, unsupported by any literature or patent publications, that "[t]he amounts of active agent (ocinaplon) to be used in each portion, the pharmaceutical carriers (e.g., lactose), and the

particle size are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and each portion can be formulated with the same active agent contained therein". (Office Action at p. 5).

Applicants respectfully traverse the foregoing grounds for rejection asserted by the Office and submit that the teachings of Media Release in combination with Hirsh et al. neither disclose nor suggest the subject matter of the instant claims.

Media Release is recognized by the Office as failing to describe the instantly claimed subject matter in a number of important aspects. In particular, Media Release provides a one sentence report of "positive safety and efficacy results" for a phase II trial of ocinaplon in "two controlled-release formulations.". No information is included in the subject Media Report pertaining a dosage form of ocinaplon comprising two separate compartments each containing ocinaplon with specific amounts with rapid release in first compartment and sustained release in second compartment with hydrophilic polymeric matrix" (quoting Office Action with respect to omissions noted in Media Release by the Office).

The record in the instant application fails to establish any direct suggestion or "practical" motivation in the prior art t hat would have led a person of ordinary skill in the art to develop the instantly claimed technology for delivering ocinaplon to treat anxiety. The cited teachings by Hirsh et al., which notably relate to a pending patent application and as such are not yet entitled to any presumption of validity, are only partially represented by the Office in the context of allegedly teaching a "new pharmaceutical composition in unit dosage form comprising anxiolytic in two different portions."

In fact, Hirsh et al. purports to provide "[a] pharmaceutical composition in unit dosage form for ANY ("at least one") "pharmaceutically active ingredient" (pending claim 1). The vast breadth of these unfounded teachings will be readily appreciated with reference to pending claim 28, which purports to embrace within the subject invention of Hirsh et al. the following laundry list of drugs:

> analgesics, antihistamines, antidiarrheals, anxiolytics, hypnotics, stimulants, cardiovascular drugs, pulmonary drugs, anti-hypertensives, anti-emetics, anti-inflammatory drugs, renal drugs, steroids, drugs for neurological disorders, anti-psychotic drugs, drugs for treating endocrine disorders, drugs for promoting immunology, drugs for treating osteoarthritis, drugs for treating glaucoma, drugs for treating allergic rhinitis, drugs for treating anemias and other hematological disorders, drugs for treating infectious diseases, drugs for the treatment and symptoms of cancer, drugs for insomnia, and antidiabetic drugs.

Accordingly, to accept the Office's position with respect to alleged teachings of Hirsh et al. pertaining to "dosage form comprising anxiolytic", a person of skill in the art would necessarily also construe Hirsh et al. as describing and enabling a useful, safe and effective dosage form for each of the foregoing classes of pharmaceutical agents as well. That is, Hirsh et al. would necessarily be construed as precluding all patents for dosage forms of any kind comprising "two different portions", and virtually all modes of non-"immediate" delivery achieved by such dosage forms (e.g., "sustained release", "delayed release", "slow release", "gradual release", "extended release", "controlled release", "modified release", "pulsatile release"). This position is contrary to fundamental principals in the art--that drugs of different classes, and even drugs within a particular class, exhibit widely divergent and highly unpredictable biological activities and pharmacokinetic properties. Based on these principals, it is not scientifically reasonable to interpret such vague and unfounded teachings as provided by Hirsh et al. as allegedly describing and placing into the hands of the public such unpredictable technology, spanning so vast a breadth of subject matter, as advocated by the Office.

Further contrary to the Office's position, Hirsh et al. provides no working examples of any kind of "anxiolytic" formulation. Rather, the examples of Hirsh et al. are limited to combinations of (example 1) analgesics; (example 2) hypnotics; (example 3) anti-migraine drugs; (example 4) antihistamine/decongestant drugs; and (example 5) analgesics.

In addition, Hirsh et al. actually teaches away from the subject matter of the current invention, in that all of the working examples provided by Hirsh et al. of a "two portion" (outer layer and inner core) dosage forms are comprised of two separate drugs, which are each delivered in a separate phase of a distinct, bi-phasic delivery modality.

More specifically, the examples of Hirsh et al. are described as yielding the following, bi-phasic delivery modalities from a two drug dosage form

[Example 1; § 88] "The dosage preparation provides two consecutive doses of analgesic agents. Butorphanol and Rofecoxib. Butorphanol is released from the outer layer intraorally to provide a rapid onset and to avoid first pass metabolism. Rofecoxib is released 2 to 4 hours later to provide a continuous analgesic activity for additional approximately 24 hours."

[Example 2; § 108] "The dosage preparation provides two consecutive doses of a hypnotic agent. The first dose of Zolpidem is released from the outer layer intraorally to provide a rapid onset and to avoid first metabolism and a second dose is released 0.5 to 2

hours later to provide a continuous hypnotic activity for a total of approximately 6 to 10 hours."

[Example 3; § 125] "The dosage preparation provides administration of Ergotamine intraorally for a rapid onset and to avoid first pass metabolism. The dosage form also provides a second drug, Caffeine which is released after oral administration of the dosage form."

[Example 4; § 150] "The dosage preparation provides two consecutive doses of antihistamines, chlorpheniramine and loratadine which release about 4 to 6 hours apart."

[Example 5; § 170] "The dosage preparation provides two consecutive doses of analgesic agents, Fentanyl and morphine. . . . Fentanyl provides a rapid onset of analgesia lasting approximately 2 hours, after which the orally ingested morphine which was formulated with a 2 hour delayed release provides sustained release analgesia for 8 to 12 hours."

Applicants respectfully submit that these distinct descriptions teach directly away from providing a "two portion" dosage form for a single drug, and most certainly do not practically teach nor suggest such two portion dosage form as an obvious modification of Media Release (teaching only a "controlled release" delivery mode).

Further in this context, the record is also deficient to support the proposed modification of Media Release (i.e., to employ a two portion dosage form), on the basis that "Media Release II (R & D Focus Drug News 2 Dec 2002; made of record with Office Action) similarly cites positive phase two results for "an immediate release formulation of ocinaplon". The Office provides no basis for distinguishing the cited Media Release (relating to "controlled release" ocinaplon), and Media Release II (relating to immediate release ocinaplon), that would evince a preference to investigate and develop controlled release ocinaplon dosage forms.

The general motivation cited by the Office, i.e., that all "two portion" dosage forms contemplated by Hirsh et al., the full vast assemblage of drugs contemplated by Hirsh et al., would allegedly provide the purported benefits of providing "immediate as well as sustained release to improve prolonged therapeutic benefit and improve the compliance" (id.) There is no foundation in the record for this blanket assessment of the alleged benefits of a two portion dosage form—i.e., as applying to a huge assemblage of drugs having divergent and unpredictable biological activities and pharmacokinetic properties, for an equally broad array of treatment indications mediated by distinct biochemical mechanisms and affected by diverse physiological processes.

The record clearly fails to satisfy the Office's burden of providing direct, scientific evidence to establish a prima facie case of obviousness. In this context, the Federal Circuit's predecessor court held in In re Gyurik, 201 USPQ 552, 557 (CCPA 1979) that:

> An element in determining obviousness of a new chemical compound is the motivation of one having ordinary skill in the art to make it. *That motivation is not abstract, but practical, and is always related to the properties or uses one skilled in the art would expect the compound to have, if made.* (emphasis supplied).

Applying this authority to the present facts, the two Media Releases have not been shown by the Office as distinct in terms of favoring either "immediate release" or "controlled release" dosage forms of ocinaplon. Accordingly, the full spectrum of dosage forms and delivery modalities essentially remained to be mapped out and tested at the time of Applicants' invention. No "practical" motivation to select a particular (even general) pathway for future development is specified by the Office. In fact, the teachings of Hirsh et al., discussed above, have been shown to be inapposite to the instant invention, because they relate to bi-modal delivery of different drugs. Therefore, the proposed combination, i.e., to modify a "controlled release" ocinaplon dosage form as allegedly described in Media Release, to construct a "two portion" dosage form (actually a bi-modal delivery dosage form comprising, in the limited working embodiments, two separate drugs in an outer layer and inner core) is unsubstantiated by scientific evidence in the record. The cited references provide insufficient motivation and guidance to support the instant rejection under 35 USC § 103. As Applicants have construed these references, it can be fairly said that they in fact "teach away" from the instant invention. Most certainly, the combined references fail to establish that persons of ordinary skill in the art would have been practically motivated to develop Applicants' novel dosage forms for ocinaplon with a reasonable expectation that such dosage forms would achieve the "particular results" described by Applicants. (See, e.g., *Interconnect Planning Corp. v. Feil*, 227 USPQ 543, Fed. Cir. 1985, wherein the panel held that it is "critical" for the Office to consider "the particular results achieved by the new combination . . . ." in determining obviousness or nonobviousness).

Because the foregoing remarks establish that the instant rejection of claims is overcome, Applicants decline address the more specific merits of rejection. Nonetheless, Applicants respectfully submit that the record is likewise deficient for failure to evince that "[t]he amounts of active agent (ocinaplon) to be used in each portion, the pharmaceutical carriers (e.g., lactose), and the particle size are all deemed obvious since they are all within the

knowledge of the skilled pharmacologist and each portion can be formulated with the same active agent contained therein". (Office Action at p. 5). Here, it is likewise apparent that the blanket assertions by the Office (e.g., alleging that essentially all dosages for all drugs, in all conceivable dosage forms including two portion dosage forms, is within the knowledge of the ordinarily skilled pharmacologist) are unsupported by actual evidence in the record, and are contrary to fundamental principles of pharmacology.

In view of the foregoing evidence and authority, Applicants respectfully submit that the rejection of claims 12-21 under 35 USC § 103(a) as allegedly unpatentable over Media Release (Novermber 4, 2002) in view of Hirsh et al. (US 2003/0035839 A1) has been overcome.

Additionally, Applicants reserve the right to present evidence, e.g., by way of a Declaration under 37 CFR § 1.131, showing that the cited reference Media Release was published by or on behalf of the instant inventors less than a year before the priority date of the instant application, and/or that the invention was conceived by the instant inventors prior to the date of this publication.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at (425) 455-5575.

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Respectfully submitted,

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